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09/744,431	01/22/2001	James Arthur Hoffmann	X-12383M	5086

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ELI LILLY AND COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/744,431	Applicant(s) HOFFMANN ET AL.	
	Examiner Regina M. DeBerry	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *141-158* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *141-158* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Am ndments and/or Claims

The amendment filed 07 January 2003 (Paper No. 12) has been entered in full. Claims 92-106 and 110-117 were cancelled. New claims 141-158 were added. Claims 141-158 are under examination.

The information disclosure statement filed 07 January 2003 (Paper No. 13) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The claim to priority has been met.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The objection to the specification as set forth at page 3 of the previous Office Action (03 July 2002, Paper No. 10) is *withdrawn* in view of the amendment (07 January 2003, Paper No. 12).

The objection to claim 116 as set forth of page 3 of the previous Office Action (03 July 2002, Paper No. 10) is *withdrawn* in view of the amendment (07 January 2003, Paper No. 12).

The rejection of claim 100 under 35 USC 112, second paragraph as set forth of page 3 of the previous Office Action (03 July 2002, Paper No. 10) is *withdrawn* in view of the amendment (07 January 2003, Paper No. 12).

The rejection of claims 92-99, 103, 105, 112-115 under 35 USC 103(a) as being unpatentable over Skrabanja *et al.*, EP 0853 945 A1 in view of L'Italien *et al.*, US Patent No. 6,136,784 as set forth at pages 4-6 of the previous Office Action (03 July 2002, Paper No. 10) is *withdrawn* in view of the amendment (07 January 2003, Paper No. 12).

The rejection of claims 100 and 101 under 35 USC 103(a) as being unpatentable over Skrabanja *et al.*, EP 0853 945 A1 in view of L'Italien *et al.*, US Patent No. 6,136,784 and further in view of Carey *et al.*, US Patent No. 4,746,508 as set forth at pages 6-7 of the previous Office Action (03 July 2002, Paper No. 10) is *withdrawn* in view of the amendment (07 January 2003, Paper No. 12).

The rejection of claims 102, 104, 106 under 35 USC 103(a) as being unpatentable over Skrabanja *et al.*, EP 0853 945 A1 in view of L'Italien *et al.*, US Patent No. 6,136,784 and Carey *et al.*, US Patent No. 4,746,508 and further in view of Boime *et al.*, US Patent No. 6,238,890 as set forth at pages 7-8 of the previous Office Action (03 July 2002, Paper No. 10) is *withdrawn* in view of the amendment (07 January 2003, Paper No. 12).

The rejection of claims 116 and 117 under 35 USC 103(a) as being unpatentable over Arpaia *et al.*, US Patent No. 5,128,453 in view of Clark *et al.*, US Patent No. 5,374,620 and Skrabanja *et al.*, EP 0853 945 A1 as set forth at pages 6-7 of the previous Office Action (03 July 2002, Paper No. 10) is *withdrawn* in view of the amendment (07 January 2003, Paper No. 12).

Matter of Record

Applicant has addressed the rejections of claims 92-106 and 110-117 made under 35 USC 103(a). Claims 92-106 and 110-117 were cancelled, making the rejections moot. The Examiner will address Applicant's argument as it applies to claims 141-158.

Claim Rejections - 35 USC § 103

Claims 141, 142, 145, 147, 152, 154, 156 and 158 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andya *et al.*, US Patent No. 6,267,958 B1.

Andya teaches a stable lyophilized protein formulation which when reconstituted generates a stable multi-use formulation (column 1, lines 52-column 2, line 9). Andya teaches that the reconstituted formulation may be used as a multi-use formulation (column 2, lines 20-30). Andya teaches methods for preparing a stable isotonic reconstituted formulation comprising reconstituting a lyophilized mixture of a protein and a lyoprotectant in a diluent (column 3, lines 4-11) or methods for preparing a formulation comprising lyophilizing a mixture of a protein and a lyoprotectant and reconstituting the lyophilized mixture in a diluent (column 3, lines 11-23). Andya teaches an article of manufacture comprising a container which holds a lyophilized mixture of a protein and a lyoprotectant and instructions for reconstituting the lyophilized mixture with a diluent. The article of manufacture may further comprise a second container which holds a diluent (column 3, lines 22-31).

Andya teaches follicle-stimulating hormone (FSH) as a suitable protein in the formulation (column 6, lines 44-50). Andya defines "stable formulation" where the protein essentially retains its physical and chemical stability and integrity upon storage (column 8, lines 45-47). Andya discloses storage times and temperatures which overlap with the instant claims (column 8, lines 52-67). Andya teaches that a preservative can be added to the diluent to reduce bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation. Examples of preservatives include benzyl alcohol and m-cresol (column 9, lines 46-58).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Andya to make the instant invention of stable, pharmaceutical acceptable, solution formulation suitable for multi-use comprising FSH, benzyl alcohol or m-cresol. The motivation and expected success is provided by Andya who teaches stable pharmaceutical multi-use formulations and discloses FSH as a suitable protein for use in the formulation. Andya also teaches that a preservative, such as benzyl alcohol or m-cresol, can be added to the diluent to reduce bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation.

Claims 143, 146, 149-155, 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andya *et al.*, US Patent No. 6,267,958 B1 in view of Skrabanja *et al.*, EP 0853 945 A1 (cited in IDS, reference #BF). The teachings of Andya *et al.* are

described above. Andya does not explicitly state that FSH is human. Andya does not explicitly teach cartridges or concentrations of FSH recited in the instant claims.

Skrabanja teaches a stable formulation comprising liquid FSH (abstract; page 3, lines 15-18, 35-38 and page 4, lines 11-13). FSH includes all forms including recombinant FSH (page 3, lines 51-54) urinary FSH (page 3, lines 44-54) and human FSH (page 3, lines 39-40, claim 10). Skrabanja teaches various buffers (page 4, lines 41-54). Skrabanja teaches concentrations of FSH which overlap the concentrations in the instant claims (page 5, lines 9-14). Skrabanja teaches an article of manufacture comprising a vial or a pen-injector device. The formulation can be in the form of a cartridge for multiple uses (page 5, lines 21-45). Skrabanja teaches the use of the composition to treat infertility (claim 15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Skrabanja to make the instant invention of stable, pharmaceutical acceptable, solution formulation suitable for multi-use comprising FSH and benzyl alcohol. The motivation and expected success is provided by Skrabanja and Andya. Skrabanja teaches the concentrations of FSH and that various forms of FSH in can be used in stable multi-use liquid pharmaceutical formulations. Andya teaches stable pharmaceutical multi-use formulations and discloses FSH as a suitable protein and benzyl alcohol as a preservative to reduce bacterial action in multi-use reconstituted formulations.

Claims 144, 148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andya *et al.*, US Patent No. 6,267,958 B1 and Skrabanja *et al.*, EP 0853 945 A1 and further in view of Boime *et al.* US Patent No. 6,238,890 (reference cited by Examiner in the last Office Action). The teachings of Andya *et al.* and Skrabanja *et al.* are described above. Andya and Skrabanja do not teach stable pharmaceutical multi-use formulations comprising FSH variant of the formula α-subunit: (SEQ ID NO:5) and β-subunit: (SEQ ID NO:11).

Boime teaches the amino acid sequences of SEQ ID NO:5 and SEQ ID NO:11. Boime states that the α and β-subunits of the wild type heterodimers or their variants or their fragments are covalently linked, optionally through a linker moiety (abstract). Boime describes single-chain forms of heterodimers or homodimers (column 4, lines 17-30 and 47-51).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Andya and Skrabanja cited above to use the teachings of Boime to make the instant pharmaceutical invention. The motivation and expected success is provided by Andya who teaches the use of benzyl alcohol and m-cresol in stable multi-use formulations comprising FSH. Skrabanja teaches that different forms of FSH can be used in the formulations including analogs, recombinant, modified glycosylated and other forms. Boime teaches that single chain forms are unique starting materials for identifying truncated forms with the activity of the dimers and using variants of the β subunit of FSH will also help identify agonists and antagonist of the glycoprotein hormone activity.

Applicant's arguments have been fully considered but not deemed persuasive. The Andya patent teaches the use of benzyl alcohol as a preservative in stable pharmaceutical multi-use liquid formulations comprising FSH. Andya teaches the anti-bacterial properties of benzyl alcohol. Andya does not specifically say stability when describing the properties of benzyl alcohol, however, a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). The Andya patent teaches FSH as a suitable protein in stable multi-use liquid formulations. Applicant cites art regarding the stability of various heterodimeric proteins, but the art does not teach against using benzyl alcohol in formulations comprising FSH.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 141-143, 145, 146, 147, 149-152, 154, 156 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 62-78 of copending Application No. 09/973918 in view of

Andya *et al.*, US Patent No. 6,267,958 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the instant application are drawn to a stable, pharmaceutically acceptable, solution formulation suitable for multi-use comprising FSH or an FSH variant, containing an alpha and a beta subunit and preservatives, benzyl alcohol or m-cresol.

The claims of application 09/973918 are drawn to an article of manufacture comprising a vial comprising lyophilized human FSH; an aqueous diluent comprising benzyl alcohol and packaging material comprising a label that includes instructions to reconstitute the FSH with the aqueous diluent.

The claims in the instant application and in application 09/973918 recite pharmaceutical compositions comprising the same range of concentrations of FSH, human FSH and FSH produced through the use of recombinant technology. The claims in the instant application and application 09/973918 recite the same preservative, benzyl alcohol. The claims in the instant application and application 09/973918 both recite a vial lyophilized FSH and a second vial comprising a preservative, benzyl alcohol. Lastly, the instant claims recite "sufficiently stable to provide a multi-dose pharmaceutical product". The claims of application 09/973918 recite "solution which may be held or used over a period of 24 hours or greater".

The claims in the instant application do not recite a specific concentration of benzyl alcohol. However, the adjustment of concentration ratios is deemed merely a matter of judicious selection and routine optimizations, which is well within the purview of the skilled artisan. In addition, the instant claims nor the claims of application

09/973918 disclose new and/or unexpected results because of benzyl alcohol concentrations. It is noted that written descriptions are not given patentable weight, since written material is a form of intellectual property protected by copyright, not patents. Furthermore, it would be obvious to provide written instructions regarding doses, storage, etc with a pharmaceutical composition. Thus it would be obvious to design the pharmaceutical composition of claims 141-143, 145, 146, 149-152, 154, 156 because a similar composition is encompassed by the invention of application 09/973918.

Andya teaches an article of manufacture comprising a container which holds a lyophilized FSH and instructions for reconstituting the lyophilized mixture with a diluent. The article of manufacture may further comprise a second container which holds a diluent. Andya teaches that benzyl alcohol or m-cresol can be added to the diluent, thus facilitating the production of a multi-use reconstituted formulation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 144 and 148 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 62, 67, 68 and 72 of copending Application No. 09/973918 in view of Boime *et al.*, US Patent No. 6,238,890. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The claims in the instant application are drawn to a stable, pharmaceutically acceptable, solution formulation suitable for multi-use comprising FSH or an FSH variant, containing an alpha (SEQ ID NO:5) and a beta subunit (SEQ ID NO:11) and a preservative, benzyl alcohol. The claims of application 09/973918 are drawn to an article of manufacture comprising a vial comprising lyophilized human FSH; an aqueous diluent comprising benzyl alcohol and packaging material comprising a label that includes instructions to reconstitute the FSH with the aqueous diluent.

The claims in the instant application and in application 09/973918 recite pharmaceutical compositions comprising FSH and benzyl alcohol. The instant claims recite "sufficiently stable to provide a multi-dose pharmaceutical product". The claims of application 09/973918 recite "solution which may be held or used over a period of 24 hours or greater". It would be obvious to provide written instructions regarding doses, or storage with a pharmaceutical composition. Boime teaches the amino acid sequences of SEQ ID NO:5 and SEQ ID NO:11.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 153, 155 and 157 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 62, 67, 68 and 72 of copending Application No. 09/973918 in view of Skrabanja *et al.*, EP 0853 945 A1. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The claims in the instant application are drawn to a stable, pharmaceutically acceptable, solution formulation suitable for multi-use comprising FSH or an FSH variant, containing an alpha and a beta subunit and a preservative, benzyl alcohol in an cartridge. The claims of application 09/973918 are drawn to an article of manufacture comprising a vial comprising lyophilized human FSH; an aqueous diluent comprising benzyl alcohol and packaging material comprising a label that includes instructions to reconstitute the FSH with the aqueous diluent.

The claims in the instant application and in application 09/973918 recite pharmaceutical compositions comprising FSH and benzyl alcohol. The instant claims recite "sufficiently stable to provide a multi-dose pharmaceutical product". The claims of application 09/973918 recite "solution which may be held or used over a period of 24 hours or greater". It would be obvious to provide written instructions regarding doses, or storage with a pharmaceutical composition. Skrabanja teaches stable multi-use liquid pharmaceutical formulations comprising FSH stored in cartridges. Skrabanja teaches the use of the composition to treat infertility (claim 15).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 141-152, 154, 156, 158 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 104-115, 120-127 of copending Application No. 09/928,198 in view of Andya *et*

al., US Patent No. 6,267,958 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The claims of the instant application are drawn to a stable, pharmaceutically acceptable solution formulation suitable for multi-use comprising FSH or an FSH variant, containing an alpha and a beta subunit and preservatives benzyl alcohol or m-cresol.

The claims of application of 09/928,198 are drawn to a pharmaceutically acceptable formulation comprising FSH or FSH variant and benzyl alcohol sufficiently stable to provide a multi-dose pharmaceutical product.

The claims in the instant application and in application 09/928,198 recite pharmaceutical compositions comprising the same preservative, benzyl alcohol and the same α-subunit (SEQ ID NO:5) and β-subunit (SEQ ID NO:11). The claims in the instant application and in application 09/928,198 both recite pharmaceutical compositions comprising human FSH, the same concentration of FSH and multi-dose pharmaceutical products.

Andya teaches stable, pharmaceutically acceptable solution formulation suitable for multi-use comprising FSH and a preservative benzyl alcohol and m-cresol. Andya teaches an article of manufacture comprising a container which holds a lyophilized mixture of a protein and a lyoprotectant and instructions for reconstituting the lyophilized mixture with a diluent. The article of manufacture may further comprise a second container which holds a diluent. Thus it would be obvious to design the pharmaceutical

composition of claims 141-146, 148-152, 154, 156, 158 because a similar composition is encompassed by the invention of application 09/928,198.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 153, 155 and 157 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 104-111 of copending Application No. 09/928,198 in view of Skrabanja *et al.*, EP 0853 945 A1. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the instant application are drawn to a stable, pharmaceutically acceptable solution formulation suitable for multi-use comprising FSH or an FSH variant, containing an alpha and a beta subunit and a preservative benzyl alcohol in a cartridge and a method of treating fertility with the instant composition.

The claims of application of 09/928,198 are drawn to a pharmaceutically acceptable formulation comprising FSH or FSH variant and benzyl alcohol sufficiently stable to provide a multi-dose pharmaceutical product.

Skrabanja teaches stable multi-use liquid pharmaceutical formulations comprising FSH stored in cartridges. Skrabanja teaches the use of the composition to treat infertility.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Art of Record

The art made of record and not relied upon is considered pertinent to applicant's disclosure. Rinella, US Patent No. 6,440,930 B1 teaches stable, soluble formulations comprising a medically useful peptide or protein, a hydrophobic preservative, and nicotinamide. The storage-stable soluble formulation is useful as a multi-use pharmaceutical product (abstract). The hydrophobic preservatives include benzyl alcohol (column 2, lines 49-60). Medically useful proteins include follicle-stimulating hormone (FSH) (column 3, line 64-column 4, line 40).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

RMD

RMD
April 11, 2003